

Lymphadenopathy

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Lymphadenopathy, or abnormal enlargement of lymph nodes, is a common presenting finding in several diseases, occurring in approximately 0.5% of the general population each year. Lymph nodes enlarge due to normal reaction to infection, abnormal inflammatory response, or neoplasia (Table 30-1). The differential diagnosis for lymphadenopathy is very broad and requires an initial thorough history and physical examination, followed by indicated testing.

Signs

- In children, palpable lymph nodes are common, even without evidence of disease.
- In healthy infants, lymph nodes greater than 0.3 cm in diameter are palpated in either cervical, axillary, or inguinal sites. ++++
- Healthy children 3 weeks to 6 years old may have palpable lymph nodes 0.5 cm or larger in cervical, occipital, submandibular, or postauricular sites (descending order of prevalence). ++++
- Patients older than 40 to 50 years are much more likely than those younger to have a neoplastic cause for lymphadenopathy.

Workup

- Detailed history and physical examination
 - Attention to constitutional, respiratory, dermatologic, and neurologic symptoms
 - Investigate medications, history of travel, HIV risk factors, or animal exposures.
 - Measure weight and height (in children plot against growth curves).
 - Note number, size, location, consistency, tenderness, and mobility of palpable nodes.
- Investigations to consider
 - Basic screening labs—CBC with differential, ESR, LDH, uric acid, and LFTs
 - Epstein-Barr virus (EBV), CMV, HIV and/or *Bartonella henselae* titers (if initial workup suggests)
 - Chest x-ray
 - PPD
 - US—To define suppurative lymphadenitis and select aspiration or biopsy
 - CT scan—To distinguish head and neck congenital cysts from lymphadenopathy

Table 30-1. Lymphadenopathy Differential Diagnosis and Lymph Node Acuity

	ACUTE LYMPHADENOPATHY (<3 WK)	CHRONIC LYMPHADENOPATHY (>6 WK)
Normal reaction to infection	Bacterial lymphadenitis <ul style="list-style-type: none"> • <i>Staphylococcus aureus</i> • Streptococcal • Peptostreptococci • Gram-negative rods • Tuberculosis • Atypical Mycobacterium • Tularemia Reactive lymphadenitis <ul style="list-style-type: none"> • Viral URIs • Group A streptococcal pharyngitis Mononucleosis <ul style="list-style-type: none"> • EBV • CMV Cat scratch disease	Viral <ul style="list-style-type: none"> • EBV • CMV • HIV Bacterial <ul style="list-style-type: none"> • Tularemia • <i>Yersinia</i> • Tuberculosis • Atypical Mycobacterium • Cat scratch disease Fungal <ul style="list-style-type: none"> • Histoplasmosis • Coccidioidomycosis Other <ul style="list-style-type: none"> • Toxoplasmosis
Abnormal response to inflammation	Kawasaki's disease (children) Serum sickness Vaccination reactions Drug hypersensitivities <ul style="list-style-type: none"> • Allopurinol • Aspirin • Anticonvulsants (phenytoin) • Antibiotics (sulfa, PCN) 	Autoimmune disorders <ul style="list-style-type: none"> • Sarcoid • Systemic lupus erythematosus • Rheumatoid arthritis • Sjögren syndrome • Amyloidosis Vaccination reactions Drug hypersensitivities
Neoplasia	Acute leukemias	Lymphoma <ul style="list-style-type: none"> • Hodgkin's • Non-Hodgkin's Lymphoproliferative disorders Leukemia (acute or chronic) Solid tumor metastasis

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; PCN, penicillin; URI, upper respiratory infection.

- Needle aspiration—To evaluate fluid with Gram stain, acid-fast stain, and aerobic/anaerobic culture
- Lymph node biopsy—The definitive test to evaluate for neoplastic causes
 - Consider if lymphadenopathy is extensive (generalized or >2 cm in diameter) or associated with other concerning findings on history and physical examination (Table 30-2)

Table 30-2. Concerning ("Red Flag") Findings with Lymphadenopathy

SIGNS AND SYMPTOMS	ASSOCIATED DISORDER(S)
Splenomegaly	Mononucleosis Neoplasia (lymphoma, leukemia)
"B" symptoms Fever Night sweats Weight loss (>10% unexplained)	Tuberculosis HIV Neoplasia (lymphoma, leukemia, solid tumor metastasis)
Pruritus	Neoplasia (lymphoma, leukemia) Autoimmune disorders (SLE, RA)
Chest/hilar lymphadenopathy	Community-acquired pneumonia Tularemia Psittacosis Pertussis Tuberculosis Coccidioidomycosis Histoplasmosis Neoplasia (lymphoma, lung, breast, gastrointestinal)
Abdominal lymphadenopathy	Neoplasia (lymphoma, leukemia, gastric, or bladder) Tuberculosis

HIV, Human immunodeficiency virus; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus.

- Available prediction rules for the need of biopsy require further validation.
- Nonspecific or nondiagnostic results are common; sometimes repeat biopsy is indicated.

Comments and Treatment Considerations

With only a few exceptions, a lymphadenopathy site does not predict etiology. Head and neck nodes are more frequently associated with localized infectious or inflammatory conditions than malignancy. Extremity nodes often occur in response to peripheral infections (i.e., cellulitis). Supraclavicular, mediastinal, or abdominal lymphadenopathy, however, should be considered neoplastic until proven otherwise.

Based on size alone, lymph node diameter does not reliably distinguish neoplastic or inflammatory causes from more common infectious causes, although lymph nodes less than 1 cm in size are rarely from neoplastic causes. A study of healthy infants found no lymph node enlarged more than 1.2 cm in diameter in neonates or 1.6 cm in older infants. In adults, large lymph nodes are less common but are more likely associated with malignancy. One study found that 8% of adults with unexplained enlarged lymph nodes between 1.0 and 2.25 cm in diameter were eventually found to have a neoplastic cause.

The acuity of lymph node enlargement may suggest certain diseases. Lymphadenopathy has been defined as acute if it lasts less than 3 weeks and chronic if lasting longer than 6 weeks. Acute lymphadenopathy is commonly caused by a normal reaction to localized infection (i.e., pharyngitis), generalized infection (i.e., EBV), or primary lymph node infection (i.e., bacterial lymphadenitis) (see [Table 30-1](#)). Chronic lymphadenopathy has a very broad differential diagnosis, sometimes resulting in lymph node biopsy to diagnose. Significant overlap in the duration of the various causes does not reliably distinguish a cause based solely on lymph node acuity. Still, when significant lymph node enlargement is found in its early stages, the more common infectious causes should be considered and if not resolved in an expected duration, chronic causes should also be considered.

CAT SCRATCH DISEASE

Symptoms

- Fever—Sometimes prolonged
- Painful lymph nodes draining from extremity of exposure to cat scratch or bite

Signs

- Lymphadenopathy
 - Starts about 1 to 2 weeks after cat exposure, lasts 2 to 3 weeks and shrinks over 1 to 2 months
- Hepatosplenomegaly in severe cases

Workup

- Antibodies to *B. henselae*
- Polymerase chain reaction (PCR) to *B. henselae*

Comments and Treatment Considerations

Usually a self-limited disease—Antibiotic treatment (e.g., rifampin, azithromycin, ciprofloxacin, and TMP-SMX) is not routinely advised unless hepatomegaly exists, nodes are exquisitely tender, or the patient is immunocompromised. Control fever and lymph node pain with antipyretics and analgesics. Exquisitely tender nodes may require needle aspiration or excision.

HUMAN IMMUNODEFICIENCY VIRUS

Symptoms

- “B symptoms”
 - Weight loss
 - Fever
 - Night sweats
- Opportunistic infections (e.g., mycobacterial, fungal)
- Recurrent infections

Signs

- Generalized lymphadenopathy
- Mediastinal or abdominal lymphadenopathy

Workup

- ELISA and Western blot antibody testing
- CD4 counts and HIV viral load assays
- Lymph node biopsy if dominant lymphadenopathy found
 - HIV infection increases risk of mycobacterial infections and lymphomas

Comments and Treatment Considerations

The goal of treatment is early and total suppression of viral replication with HAART using protease inhibitors (PIs), nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and entry inhibitors (EIs).

CD4 counts and viral loads are followed periodically. Antimicrobial prophylaxis is no longer routinely used.

Patients with HIV often develop a nonspecific generalized lymphadenopathy that is chronic and asymptomatic. If lymphadenopathy progresses or “B symptoms” are present, evaluation for coexisting infections or neoplasia may be needed.

Evaluate and treat HIV patients in conjunction with specialist who is expert and up-to-date on HIV treatments.

LYMPHADENITIS/LYMPHANGITIS**Symptoms**

- Rapid onset of painful isolated mass ++++
- Fever
- Associated infection in region of lymph drainage ++++
- With lymphangitis—Radiation of pain from site of infection to lymph node

Signs

- Isolated, tender, and enlarged lymph node +++++
 - Overlying erythema and warmth
- With lymphangitis—Red streaking from infection site toward lymph drainage

Workup

- Physical examination for site of originating infection
- US of mass if suppurative node suspected
- CT of neck if suppurative node confirmed on head or neck to distinguish from other head or neck masses
- Needle aspiration and analysis if suppurative node confirmed

Comments and Treatment Considerations

If symptoms and signs in children are consistent with lymphadenitis, treat with antibiotics because lymphadenitis is the most common

cause for these findings. Choose antibiotics covering a spectrum of the originating source of infection. An initial complete evaluation with further investigations is indicated in adults because other infectious, inflammatory, and neoplastic causes are more common than in children, even while treatment with antibiotics is underway. Lymphangitis may be caused by malignant cells obstructing lymphatic flow; close follow-up and investigation for metastatic neoplasia are suggested if treatment is not effective.

MONONUCLEOSIS

Symptoms

- Fatigue ++++
- Sore throat +++

Signs

- Anterior and posterior lymphadenopathy (one fourth lasting as long as 6 months)
- Pharyngitis
- Splenomegaly

Workup

- Heterophile antibody test (i.e., Monospot) in those older than 4 years
- EBV serology in those less than 4 years old
- Lymph node biopsy may be needed with significantly large or hard nodes; lymphoma can be associated with EBV infection

STREPTOCOCCAL PHARYNGITIS

See Chapter 40, Sore Throat.

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